

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date
1 April 2004 (01.04.2004)

PCT

(10) International Publication Number
WO 2004/027418 A3

(51) International Patent Classification⁷: G01N 33/48

(21) International Application Number:
PCT/EP2003/010404

(22) International Filing Date:
18 September 2003 (18.09.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
02021228.8 18 September 2002 (18.09.2002) EP

(71) Applicants (for all designated States except US):
G2M CANCER DRUGS AG [DE/DE]; Paul-Ehrlich-Strasse 42-44, 60596 Frankfurt am Main (DE). FORSCHUNGSZENTRUM KARLSRUHE GMBH [DE/DE]; Hermann-von-Helmholtz-Platz 1, 76344 Eggenstein-Leopoldshafen (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): HEINZEL, Thorsten [DE/DE]; Libellenweg 10, 60529 Frankfurt am Main (DE). KRÄMER, Oliver, H. [DE/DE]; Kosestrasse 38, 60318 Frankfurt am Main (DE). GÖTTLICHER,

Martin [DE/DE]; Mareesstrasse 1, 80638 München (DE). ZHU, Ping [CN/DE]; H.-Hesse-Strasse 13, 76351 Linkenheim (DE). GOLEBIEWSKI, Martin [DE/DE]; Bernhardstrasse 9, 76131 Karlsruhe (DE). PELICCI, Pier, Giuseppe [IT/IT]; Via Emilia 10, I-20090 Opera (Milan) (IT). MAURER, Alexander, B. [DE/DE]; Rainweg 3, 61352 Bad Homburg (DE). HENTSCH, Bernd [DE/DE]; Gervinusstrasse 8, 60322 Frankfurt am Main (DE). MINUCCI, Saverio [IT/IT]; Via Don Minzoni 1, I-20090 Opera (Milan) (IT).

(74) Agents: KELLER, Günter et al.; LEDERER & KELLER, Prinzregentenstrasse 16, 80538 München (DE).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

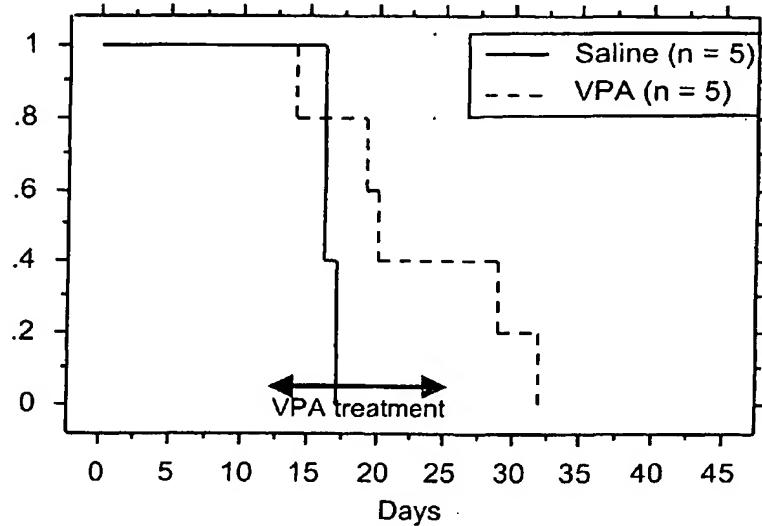
(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),

[Continued on next page]

(54) Title: THE USE OF MOLECULAR MARKERS FOR THE PRECLINICAL AND CLINICAL PROFILING OF INHIBITORS OF ENZYMES HAVING HISTONE DEACETYLASE ACTIVITY

A

Cumulative Survival



(57) Abstract: The present invention relates to the use of molecular markers and related signaling mechanisms for the preclinical and clinical profiling of inhibitors of enzymes having histone deacetylase activity. The invention also relates to the use of such markers as diagnostic and/or prognostic tools for the treatment of tumor patients with such inhibitors.

WO 2004/027418 A3



Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(88) Date of publication of the international search report:
13 May 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Published:

- *with international search report*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

INTERNATIONAL SEARCH REPORT

International Application No
PCT/03/10404A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 35990 A (JAMISON TIMOTHY F ;HARVARD COLLEGE (US); TAUNTON JACK (US); HASSIG) 2 October 1997 (1997-10-02) abstract; claims 50,63-73 ----	1-9,19, 20
X	EP 1 050 581 A (MEDICAL & BIOLOG LAB CO LTD) 8 November 2000 (2000-11-08) abstract; claims 11,12,15 ----	1-9,19, 20

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the International filing date but later than the priority date claimed

"T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the International search

Date of mailing of the International search report

9 March 2004

29/03/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

GONCALVES M L F C

INTERNATIONAL SEARCH REPORT

Intern. Application No
PCT/03/10404

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SU G H ET AL: "A NOVEL HISTONE DEACETYLASE INHIBITOR IDENTIFIED BY HIGH-THROUGHPUTTRANSCRIPTIONAL SCREENING OF A COMPOUND LIBRARY" CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, vol. 60, no. 12, 15 June 2000 (2000-06-15), pages 3137-3142, XP000985980 ISSN: 0008-5472 page 3137	1-9,19, 20
Y	KWON H-J-ET AL:—"A-histone deacetylase inhibitor, trichostatin A, induces apoptosis through suppression of anti-apoptotic factors, c-IAP-1 and c-IAP-2 in human prostate epithelial cells" PROCEEDINGS OF THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, NEW YORK, NY, US, vol. 40, March 1999 (1999-03), page 581 XP002180771 ISSN: 0197-016X abstract	1-9,19, 20
Y	SCHMIDT K ET AL: "INHIBITORS OF HISTONE DEACETYLASE SUPPRESS THE GROWTH OF MCF-7 BREAST CANCER CELLS" ARCHIV DER PHARMAZIE, VCH VERLAGSGESELLSCHAFT MBH, WEINHEIM, DE, vol. 332, no. 10, 1999, pages 353-357, XP000985303 ISSN: 0365-6233 page 354	1-9,19, 20
Y	WARELL R P ET AL: "THERAPEUTIC TARGETING OF TRANSCRIPTION IN ACUTE PROMYELOCYTIC LEUKEMIA BY USE OF AN INHIBITOR OF HISTONE DEACETYLASE" JOURNAL OF THE NATIONAL CANCER INSTITUTE, US DEPT. OF HEALTH, EDUCATION AND WELFARE, PUBLIC HEALTH, US, vol. 90, no. 21, November 1998 (1998-11), pages 1621-1625, XP002928827 ISSN: 0027-8874 abstract	1-9,19, 20
A	JUNG M: "INHIBITORS OF HISTONE DEACETYLASE AS NEW ANTICANCER AGENTS" CURRENT MEDICINAL CHEMISTRY, BENTHAM SCIENCE PUBLISHERS BV, BE, vol. 8, 2001, pages 1505-1511, XP001098704 ISSN: 0929-8673 abstract	1-9,19, 20

-/-

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US03/10404

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GREENBERG V L ET AL: "HISTONE DEACETYLASE INHIBITORS PROMOTE APOPTOSIS AND DIFFERENTIAL CELL CYCLE ARREST IN ANAPLASTIC THYROID CANCER CELLS" THYROID, MARY ANN LIEBERT, NEW YORK, NY, US, vol. 11, no. 4, April 2001 (2001-04), pages 315-325, XP009003316 ISSN: 1050-7256 abstract ---	1-9, 19, 20
Y	WO 00 71703 A (METHYLGENE INC) 30 November 2000 (2000-11-30) abstract; claims 28-39 ---	1-9, 19, 20
X	"SMALL MOLECULE INHIBITORS OF HISTONE DEACETYLASE" EXPERT OPINION ON THERAPEUTIC PATENTS, ASHLEY PUBLICATIONS, GB, vol. 12, no. 6, 2002, pages 943-947, XP001120539 ISSN: 1354-3776 page 944 -page 945 -----	1-9, 19, 20

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 10-18

Present claims 10-17 relate to a product and the uses of a product defined by reference to a desirable characteristic or property, namely "means to determine the amount of a molecular marker". The claims cover all products having this characteristic or property, whereas the application provides support within the meaning of Article 84 EPC and/or disclosure within the meaning of Article 83 EPC for only a very limited number of such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 84 EPC). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the methods of claims 1-9 and Kit of claims 19-20.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 10-18

Present claims 10-17 relate to a product and the uses of a product defined by reference to a desirable characteristic or property, namely "means to determine the amount of a molecular marker". The claims cover all products having this characteristic or property, whereas the application provides support within the meaning of Article 84 EPC and/or disclosure within the meaning of Article 83 EPC for only a very limited number of such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 84 EPC). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the methods of claims 1-9 and Kit of claims 19-20.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/10404

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: 10-18 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/10404

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 9735990	A	02-10-1997	AU WO	2990597 A 9735990 A2		17-10-1997 02-10-1997
EP 1050581	A	08-11-2000	EP WO	1050581 A1 9936532 A1		08-11-2000 22-07-1999
WO 0071703	A	30-11-2000	AU CA EP WO JP US	6718200 A 2366408 A1 1173562 A2 0071703 A2 2003500052 T 2003078216 A1		12-12-2000 30-11-2000 23-01-2002 30-11-2000 07-01-2003 24-04-2003